Title: Multiple Primary Cancers Associated with Merkel Cell Carcinoma in Queensland, Australia, 1982-2011

Short title: Multiple Primary Cancers Associated with MCC

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Key words: Merkel cell carcinoma, multiple primary cancers, ultraviolet radiation, Australia

Abbreviations: BCC – Basal cell carcinoma; CI – confidence interval; MCC – Merkel cell carcinoma; MCPyV – Merkel cell polyoma virus; SCC – Squamous cell carcinoma; UV – ultraviolet.

Article category: Research - Epidemiology

Novelty and impact: This study examines the occurrence of multiple primary cancers for people with Merkel cell carcinoma (MCC) in a population that has the highest incidence rates of MCC in the world. We were able to identify several significant associations between MCC and cancers of other sites (such as the lip, kidney, colon/rectum and prostate) that have not been previously described. Our results have the potential to influence the development of clinical practice guidelines for MCC.

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Figure count: 0
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Reference count: 38
Abstract

The relatively high incidence of Merkel cell carcinoma (MCC) in Queensland provides a valuable opportunity to examine links with other cancers. A retrospective cohort study was performed using data from the Queensland Cancer Registry. Standardised incidence ratios (SIRs) were used to approximate the relative risk of being diagnosed with another primary cancer either following or prior to MCC. Patients with an eligible first primary MCC (n=787) had more than double the expected number of subsequent primary cancers (SIR=2.19, 95% CI=1.84-2.60; p<0.001). Conversely, people who were initially diagnosed with cancers other than MCC were about two and a half times more likely to have a subsequent primary MCC (n=244) compared to the general population (SIR=2.69, 95% CI=2.36-3.05; p<0.001). Significantly increased bi-directional relative risks were found for melanoma, lip cancer, head and neck cancer, lung cancer, myelodysplastic diseases and cancer with unknown primary site. In addition, risks were elevated for female breast cancer and kidney cancer following a first primary MCC, and for subsequent MCCs following first primary colorectal cancer, prostate cancer, non-Hodgkin lymphoma or lymphoid leukaemia. These results suggest that several shared pathways are likely for MCC and other cancers, including immunosuppression, ultraviolet radiation and genetics.
Introduction

Merkel cell carcinoma (MCC) is an uncommon but aggressive form of skin cancer (Donepudi et al., 2012; Poulsen, 2004; Prieto Munoz et al., 2013; Taylor G et al., 2005). Prognosis is often poor because the tumours tend to grow rapidly with a high risk of early metastasis (Donepudi et al., 2012; Nicolaidou et al., 2012; Prieto Munoz et al., 2013).

Apart from old age, the main known risk factors for MCC are exposure to ultraviolet (UV) radiation and immunosuppression (Agelli et al., 2010; Becker, 2010; Donepudi et al., 2012; Nicolaidou et al., 2012; Poulsen, 2004; Pulitzer et al., 2009), although it is yet to be determined to what degree the latter two factors work together (Schrama et al., 2012). A predominantly viral aetiology appears likely given that a human pathogen called Merkel cell polyomavirus (MCPyV) (Feng et al., 2008; Spurgeon and Lambert, 2013) has been discovered in up to 90% of cases in North America and Europe (Donepudi et al., 2012; Prieto Munoz et al., 2013). However, there has been some speculation that sun exposure may make a greater contribution to the incidence of MCC in parts of Australia due to elevated levels of ambient UV radiation (Girschik et al., 2011). Our recent finding (Youlden et al., 2014) that the incidence rate of MCC is twice as high in Queensland than anywhere else in the world, and up to 7 times higher than rates in some countries in northern Europe may provide support for the hypothesis that a larger proportion of MCCs in Australia are sun-related.

Studies examining the occurrence of multiple cancers in the same person can contribute towards an understanding of the aetiology of cancer. While several previous international studies have reported that people diagnosed with MCC are at increased risk of other primary cancers (Brenner et al., 2001; Bzhalava et al., 2011; Gass et al., 2010; Howard et al., 2006; Kaae et al., 2010; Koljonen et al., 2010; Tadmor et al., 2012), Australia is well recognised as being a unique environment in terms of high UV exposure, outdoor lifestyle and a predominately Caucasian population. This combination of factors provides an
ideal opportunity to investigate whether people in Australia who are diagnosed with MCC are more likely than the general population to develop other sun-related cancers, thus adding to the body of evidence regarding whether MCCs are also related to sun exposure. The aim of the present work was therefore to examine the occurrence of multiple primary cancers within a large cohort of MCC patients and to determine how the results compare with other parts of the world.

Results

Study Cohorts

First primary MCC - A total of 815 cases of first primary MCC were recorded for Queensland residents between 1982 and 2010. Those who had less than two months of follow-up from the time of diagnosis (n=28) were excluded from the analysis, leaving 787 cases (97%) of first primary MCC remaining in the study. About two-thirds (65%) of these MCC patients were males and the age at diagnosis ranged from 29 to 104 with a median of 75 years old. The cohort of patients with a first primary MCC accumulated 3,377 years of follow-up in total (median=2.2 years).

Other first primary cancers – The cohort of all first primary cancers (excluding MCC) diagnosed between 1982 and 2010 included 357,753 individuals with a total follow-up of 2,308,416 years (median=4.2 years). Males (55%) outnumbered females, and the median age at diagnosis was 64 years old. More than half (55%) of the other first primary cancers were either melanoma, prostate cancer (both 14%), breast cancer or colorectal cancer (13% each).

Subsequent Primary Cancers Following a First Primary MCC

Of the 787 eligible cases of first primary MCC, 119 patients (15%) were diagnosed with a total of 135 subsequent primary cancers by the end of 2011. As shown in Table 1, the most common types of subsequent primary cancers were melanoma (15%), prostate cancer (11%), lung cancer (10%) and
People with MCC had more than double the risk (SIR=2.19, 95% CI=1.84-2.60; p<0.001) of being diagnosed with a subsequent primary cancer compared to the general population. Elevated SIRs (Table 1) were found for each of the various types of skin cancer i.e. MCC, melanoma and the grouping of other cancers of the skin (excluding basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) of the skin). There was also a significant excess of lip cancer, head and neck cancer, and cancer with unknown primary site among MCC patients, even when subsequent cancers were restricted to those diagnosed at least one year after MCC. In contrast, SIRs were only statistically significant for lung, breast and kidney cancers and myelodysplastic diseases when tumours diagnosed within the first year were included. There was no significant increase in risk for either Non-Hodgkin lymphoma or lymphoid leukaemia following a first primary MCC.

*Subsequent Primary MCCs Following a First Primary Cancer*

Between 1982 and 2011, 272 subsequent primary MCCs were diagnosed. After excluding those cases where there was less than two months after the diagnosis of the first primary cancer, where the first primary cancer was diagnosed before 1982 or after 2010, or where there were multiple records of MCC for the same person (n=28), 244 (90%) eligible cases of subsequent primary MCC remained. Again this group were predominantly males (75%) with a slightly older median age at diagnosis of subsequent primary MCCs (78 years old) compared to the first primary MCCs.

The most frequent types of first primary cancer prior to MCC were melanoma (25%), prostate cancer (16%), colorectal cancer (11%) and lip cancer (7%). Most (n=221, 91%) of the cases of MCC in the colorectal cancer (9%). About one quarter (n=30, 22%) of the subsequent cancers were diagnosed within the first 12 months of the initial MCC diagnosis and the remainder (n=105, 78%) were diagnosed 1 or more years afterwards.
study that occurred subsequent to another first primary cancer were diagnosed more than 1 year after the initial cancer.

Compared to the general population, cancer survivors were about two and a half times more likely to be diagnosed with a subsequent primary MCC (SIR=2.69, 95% CI=2.36-3.05; p<0.001). The largest relative risks occurred for patients with cancer of unknown primary site, lip cancer, and lymphoid leukaemia (all with SIR > 8; Table 2). Significant SIRs were also found following myelodysplastic diseases, melanoma, head and neck cancer, non-Hodgkin lymphoma, lung cancer, colorectal cancer and prostate cancer. Furthermore, all of these risks remained elevated when only MCCs diagnosed more than 1 year after the first primary cancer were considered. No significant association with subsequent primary MCC was observed for first primary stomach, bladder, kidney, breast or gynaecological cancers.

Discussion
In this study we have examined the occurrence of multiple primary cancers associated with MCC in a population that has the highest incidence rates of MCC in the world (Youlde

The overall increased relative risk of a subsequent malignancy among MCC patients in our study was equivalent to those reported in some of the smaller studies (Brenner et al., 2001; Kaae et al., 2010;
Koljonen et al., 2010), but considerably higher than that reported in the United States (Howard et al., 2006) (SIR=1.2) or Scandinavia (Bzhalava et al., 2011) (SIR=1.4). Only two studies (Howard et al., 2006; Kaae et al., 2010) have reported separate results for the risks of MCC following other first primary cancers. Again, the relative risk for subsequent MCCs in Queensland was much greater than in the United States (Howard et al., 2006) (SIR=1.4) but similar to Denmark (Kaae et al., 2010) (SIR=2.6). It should be noted that the results from the United States probably provide the most valid benchmark for the Queensland data because the overall SIRs from other countries have included keratinocyte cancers (BCCs and/or SCCs of the skin) which have been found to have very high SIRs (Bzhalava et al., 2011; Kaae et al., 2010; Koljonen et al., 2010) and would most likely elevate the total relative risk.

While MCC is known to occur with other cutaneous tumours and some solid tumours, the strongest associations have been found for haematological malignancies, particularly chronic lymphocytic leukaemia (Howard et al., 2006; Kaae et al., 2010; Tadmor et al., 2012). Although there was an increased bi-directional risk between MCC and total lymphohematopoietic cancers (which includes all leukaemias, lymphomas and any other neoplasms of lymphatic or hematopoietic tissue) in Queensland, we did not observe a significant SIR for either lymphoid leukaemia or non-Hodgkin lymphoma following MCC, unlike some other studies (Howard et al., 2006; Kaae et al., 2010). We did, however, find a greater than expected number of MCCs that were diagnosed after lymphoid leukaemia or non-Hodgkin lymphoma (Howard et al., 2006; Kaae et al., 2010).

Some of the strongest associations with other cancers for people in Queensland diagnosed with MCC were for sun-related tumours. Large, bi-directional relative risks were found for both melanoma and lip cancer. Significant relationships between melanoma either following (Bzhalava et al., 2011) or prior to (Howard et al., 2006; Kaae et al., 2010) MCC have been reported previously, with SIRs of a similar magnitude to those reported here.
In agreement with our findings, increased SIRs for female breast cancer (Koljonen et al., 2010) and certain types of head and neck cancer (such as cancer of the larynx (Bzhalava et al., 2011) or salivary glands (Howard et al., 2006)) have been observed by other researchers following a first primary MCC, while an excess of MCC following cancer of the respiratory organs was also found in an earlier study (Howard et al., 2006). Additionally, we found significantly increased bi-directional risks for myelodysplastic diseases and cancer with unknown primary site, as well as for kidney cancer following MCC (within the first year of diagnosis only) and for MCC after first primary colorectal and prostate cancers; none of these associations with MCC have been documented until now.

Despite breakthroughs in the understanding of MCC in recent years, much remains unknown about how it originates (Agelli et al., 2010; Nicolaidou et al., 2012; Prieto Munoz et al., 2013). Immunosuppression was identified as a risk factor for MCC following case reports for organ transplant recipients (Kempf et al., 2013) and HIV/AIDS patients (Engels et al., 2002). The subsequent discovery of MCPyV has led to a greater understanding of the pathogenesis of MCC, but the exact processes involved are yet to be determined, such as how the virus invades Merkel cells (Bhatia et al., 2011; Chang and Moore, 2012).

Investigations such as the current one are important because excesses of particular types of cancer either before and/or after a diagnosis of MCC may suggest a common aetiology, particularly when bi-directional associations are present. One such possibility is the potential involvement of MCPyV in other cancers (Bzhalava et al., 2011; Kaae et al., 2010). MCPyV is thought to have a suspected role in the pathogenesis of certain types of leukaemia and lymphoma (Pantulu et al., 2010; Teman et al., 2011). For example, mutations of the large T antigen of MCPyV have been found in the presence of both MCC and chronic lymphoid leukaemia and are thought to explain at least some of their co-occurrence (Pantulu et al., 2010). A viral mechanism may also provide a plausible explanation for the association of MCC with head and neck cancers (D'Souza and Dempsey, 2011). Our data provide support for these theoretical associations. Moreover, it has been reported that treatment with immune-suppressive agents such as purine analogs for
some pre-existing lymphoproliferative malignancies may exacerbate existing immunosuppression, thus putting patients at possible increased risk of developing MCC (Tadmor et al., 2012).

In addition, MCC may share non-viral risk factors with other tumours (Kaae et al., 2010). Of particular interest in the current study is the potential involvement of UV radiation. Given the established role of excess sun exposure in the development of melanoma (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2009), it is highly plausible (Agelli et al., 2010; Bzhalava et al., 2011; Miller and Rabkin, 1999) that this contributes to the large relative risks of being diagnosed with melanoma either before or after MCC that were observed. Furthermore, a positive association has been identified between UV radiation and lip cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2009); hence, our finding of the co-occurrence of MCC with lip cancer in Queensland may point to sun exposure as a shared cause.

Another possibility is that sunlight and MCPyV may act in combination. In particular, researchers have demonstrated that UV radiation can regulate the level of MCPyV replication, thus providing a potential explanation for the association between MCC and sun exposure (Mogha et al., 2010).

Genetic links between MCC and other cancers have also been proposed, particularly those of neuroendocrine origin (including melanoma) (Vortmeyer et al., 1998). It is feasible that some of the unexplained associations that we have reported here may have a very specific underlying genetic pathway, similar to the relationship for melanoma and kidney cancer in persons with a MITF-E318K mutation as described by Bertolotto and colleagues (Bertolotto et al., 2011).

A significant excess of head and neck cancers, female breast cancer, and kidney cancer have been previously reported among melanoma survivors in Queensland (Youlden and Baade, 2011). However, it
is not clear what, if any, aetiological links there may be between MCC, melanoma and these other types of cancer.

Caution should be exercised when interpreting and comparing relative risks as opposed to absolute risks. A main strength of our work is that it involves one of the largest, population-based groups of MCC cases available. Even with this large cohort, actual numbers of subsequent cancers are low for some cancer types, limiting our ability to examine the associations in more detail. People diagnosed with cancer are likely to have ongoing contact with medical professionals and heightened awareness of their health as a result, but it is not possible to quantify the extent to which this may have influenced our results. The fact that most of the increased relative risks remain more than 1 year after the initial diagnosis reduces the likelihood that subsequent cancers were detected primarily as a result of increased medical surveillance.

Despite improvements in clinical and histopathological diagnostic techniques, it remains difficult to distinguish MCC from other similar skin neoplasms (Jalilian et al., 2013). It is therefore possible that some cases of MCC have been incorrectly identified, and conversely, that others have been excluded, although previous studies of MCC in Australia suggest that the rate of misclassification is within acceptable bounds (< 5%) (Girschik et al., 2011; Youlden et al., 2014). Another potential limitation is that bi-directional links may not always be obvious; it is possible that cancers that exhibit an excess of subsequent MCC but which do not themselves occur more than expected following a first primary MCC may be due to the low survival rates for MCC patients, thus not allowing sufficient time for the other cancer to develop (Howard et al., 2006). Unlike some other studies, we did not have information on keratinocyte cancers (BCC and SCC), the two most common types of non-melanoma skin cancers.

In summary, the results presented here indicate that MCC co-occurs with a range of other cancers for people in Queensland at a rate that is higher than expected. The strong associations with melanoma and lip cancer are most likely caused by sun exposure, while the lack of an excess for lymphoid leukaemia or
non-Hodgkin lymphoma following MCC (in contrast to other studies) may suggest less of a viral pathway for MCC in Queensland. In addition, our findings highlight the requirement for careful and ongoing follow-up for MCC patients, particularly given that some subsequent cancers are amenable to early detection, thus increasing the prospect of successful treatment.

Material and Methods

Data

A population-based de-identified extract containing details for all cases of invasive cancer diagnosed for residents of Queensland between 1982 and 2011 was obtained from the Queensland Cancer Registry. Notification of cancers from hospitals, nursing homes and pathology services throughout the state is required by law (Queensland Cancer Registry et al., 2013). These notifications are received for every cancer diagnosed (whether primary or recurrent except for keratinocyte skin cancers) from all Queensland institutions and for Queensland residents who have moved interstate following their first cancer diagnosis. Receiving multiple notifications from these different sources permits the Queensland Cancer Registry to verify each cancer case reported. A comprehensive validation process is performed annually, with legislation allowing the Registry to query notifying institutions if information is missing or the diagnosis is questionable. Cases that are not stipulated as recurrent are classified as new primary cancers.

The extract excluded BCCs and SCCs of the skin, which are not routinely collected by most cancer registries in Australia (Queensland Cancer Registry et al., 2013). SCCs of the lip and internal body sites are reported.

MCCs were defined as ICD-O-3 code C44 and morphology code M8247/3. Two groups were studied – patients for whom MCC occurred as a first primary cancer, and those where MCC was diagnosed subsequent to another type of primary cancer. Unique dummy numbers facilitated the linkage of records
when a person had more than one primary cancer of any site. Other variables in the extract included sex, age at diagnosis, year and month of diagnosis, and year and month of death (where applicable).

First primary cancers were restricted to those diagnosed between 1982 and 2010 with data on subsequent primary cancers and/or mortality available until 31st December 2011. This potentially allowed at least one year of follow-up and a maximum of 30 years.

Any synchronous primary cancers (defined as being diagnosed within two months of the first primary cancer (Howe, 2003)) were omitted in an effort to minimise detection bias (Curtis et al., 2006). Multiple subsequent cancers of the same type were also excluded i.e. if a person had a MCC followed by two subsequent melanomas, the second melanoma was omitted.

Statistical analyses

The relative risk of being diagnosed with a subsequent primary cancer following a first primary MCC was approximated by calculating standardised incidence ratios (SIRs). This method compares the occurrence of subsequent cancers in the cohort of interest against what would be expected if the cohort experienced the same incidence rates as the general population.

The time at risk for each member of the study cohort was measured from two months after diagnosis of the first primary MCC until 31 December 2011, date of death or date of diagnosis of a subsequent cancer, whichever came first. Patients who died within two months of their initial diagnosis were effectively excluded as they did not contribute to the time at risk. The expected number of subsequent primary cancers was calculated from the product of the person years at risk and the incidence rate experienced by the total Queensland population for a particular type of cancer, stratified by sex, age group and year of diagnosis. Estimated SIRs were then obtained by dividing the observed number of cases by the expected
number. Corresponding 95% confidence intervals (CIs) and p-values were derived based on a chi-squared distribution (Breslow and Day, 1987).

This procedure was repeated after removing subsequent cancers diagnosed within the first year following the first primary MCC to determine whether any increased risks persisted for an extended period of time. Using the same methods, SIRs were also calculated for the risk of being diagnosed with a subsequent MCC after a diagnosis of any other cancer in order to investigate bi-directional risks.

All analyses were conducted using SAS v9.4 for Windows (© SAS Institute Inc., Cary, NC). Ethics approval was not required for this study because only de-identified data was used.
Conflicts of Interest

The authors state no conflict of interest.

Acknowledgments

The authors wish to thank the staff of the Queensland Cancer Registry who provided the data extract used in this study.

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References


Table 1. Standardised incidence ratios for multiple primary cancers\(^1\) following Merkel cell carcinoma, Queensland, 1982-2011.

<table>
<thead>
<tr>
<th>Type of second primary cancer (ICD-O-3 code)</th>
<th>Cancers occurring after 2 months</th>
<th>Cancers occurring after 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed number</td>
<td>Expected number</td>
</tr>
<tr>
<td>Total second primary cancers (C00-C80)</td>
<td>135</td>
<td>61.5</td>
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<tr>
<td>Total skin cancers (C44)</td>
<td>29</td>
<td>5.7</td>
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<tr>
<td>Melanoma (C44, M872-M879)</td>
<td>20</td>
<td>5.3</td>
</tr>
<tr>
<td>Merkel cell carcinoma (C44, M8247)</td>
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</tr>
<tr>
<td>Other skin (excl. BCC/SCC – C44 other)</td>
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<td>**</td>
</tr>
<tr>
<td>Total other solid tumours(^3)</td>
<td>85</td>
<td>47.1</td>
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<tr>
<td>Lip (C00)</td>
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</tr>
<tr>
<td>Head and neck (C01-C14, C30-C32)</td>
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</tr>
<tr>
<td>Stomach (C16)</td>
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</tr>
<tr>
<td>Colorectal (C18-C20, C218)</td>
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<td>9.5</td>
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<tr>
<td>Lung (C33-C34)</td>
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<tr>
<td>Breast – females (C50)</td>
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<td>Total lymphohematopoietic cancers (M959-M998)</td>
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<td>Lymphoid leukaemia (M982-M983)</td>
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<tr>
<td>Myelodysplastic cancers (M998)</td>
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<td>2.5</td>
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<tr>
<td>Unknown primary site (C80)</td>
<td>7</td>
<td>2.6</td>
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Abbreviations/Symbols: SIR = standardised incidence ratio; CI = confidence interval; excl. = excluding; ** = observed number < 5.

Notes: 1. Excludes subsequent primary cancers occurring within two months of the first primary MCC.
2. Statistically significant SIRs (p<0.05) are shown in bold.
3. Total other solid tumours excludes skin cancers (C44), lymphohematopoietic diseases (M959-M998) and cancers with unknown primary site (C80).
<table>
<thead>
<tr>
<th>Type of first primary cancer (ICD-O-3 code)</th>
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<tr>
<td>Unknown primary site (C80)</td>
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<td>0.9</td>
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</table>

Abbreviations/Symbols: SIR = standardised incidence ratio; CI = confidence interval; excl. = excluding; ** = observed number < 5.

Notes: 1. Excludes subsequent primary MCCs occurring within two months of the first primary cancer.
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